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A simple noninvasive index to predict significant liver fibrosis in patients with advanced schistosomiasis japonica☆,☆☆

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ABSTRACT

Background: Schistosoma japonicum causes marked liver fibrosis, while lethal syndromes present in advanced schistosomiasis patients. Its management depends on the degree of fibrosis present.
Patients and methods: Fifty-two patients were recruited to assess the diagnostic value of bio-markers in patients with advanced schistosomiasis japonica. Fibrosis was assessed in liver biopsies using METAVIR system. The correlation between conventional parameters and significant fibrosis (F2-F4) was assessed using univariate analysis and logistic regression. The method of area under receiver operating characteristic curves (AUROCs) was used as a measurement of diagnostic efficacy.
Results: White blood cell counts, platelet counts and albumin (all $P < 0.05$) were significantly lower, while prothrombin time, international normalized ratio (INR), hyaluronic acid (HA), IV collagen and ultrasound fibrosis scores (all $P < 0.01$) were significantly elevated in F2-F4 patients compared with F0-F1 patients. HA and INR were identified as independent predictors by multivariate analysis ($P = 0.023$ and $P = 0.013$, respectively). Of the routine laboratory tests for the diagnosis of significant fibrosis, HA gave the best AUROC of 0.875 (95% confidence interval (CI): 0.701–0.997). We constructed a new simple index (INR × HA/100) to discriminate between F2-F4 patients and F0-F1 patients. It showed the highest AUROC of 0.921 (95% CI: 0.828-1.000), and had better diagnostic values than APRI and FIB-4.
Conclusion: HA and INR were reliable markers for differentiating significant liver fibrosis in patients with advanced schistosomiasis japonica. And the new simple index can easily predict significant liver fibrosis with a high degree of accuracy.

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1. Introduction

Schistosomiasis currently affects more than 250 million people per year worldwide and results in 1.53 million disability-adjusted life years lost per annum [1]. The three major schistosome species known to infect humans are *Schistosoma haematobium* (endemic in Africa and the eastern Mediterranean), *Schistosoma mansoni* (endemic in Africa, the Middle East, the Caribbean and South America) and *Schistosoma japonicum* (endemic mainly in China, Japan and the Philippines) [2]. *S. japonicum* infection has been a major health concern in China for more than 50 years [3]. Over these past 5 decades, the estimated number of infected individuals has been reduced by extensive control measures to below 900,000, localized mainly to endemic hotspots in 5 provinces. Despite these major efforts, *S. japonicum* infection in China remains highly prevalent in existing endemic foci and the increase in the number of infections and acute cases in recent years, indicates re-emergence of schistosomiasis in other areas [4]. Further, completion of the Three Gorges Dam in 2009 is predicted to spread transmission to previously unaffected regions [5,6]. This is anticipated to increase the number of chronic infections and acute schistosomiasis cases.

S. japonicum causes marked liver fibrosis (clay pipestem fibrosis or Symmers fibrosis) associated with portal hypertension and hepatic encephalopathy, the lethal syndromes present in advanced schistosomiasis patients [2]. Despite the availability of chemotherapy with praziquantel, liver fibrosis remains among the most serious sequelae of chronic schistosome infection, occurring in up to 20% of infected individuals [7]. The management of advanced hepatic schistosomasis

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depends on the degree of liver fibrosis and whether or not cirrhosis has developed [8].

Although liver biopsy is the gold standard for the assessment of fibrosis, it has several disadvantages such as poor patient compliance, morbidity, mortality, sampling error, limited usefulness for dynamic surveillance, poor intra- and inter-observation concordance [9,10]. Ultrasonography has been used extensively for the assessment of liver morbidity in hepatic schistosomiasis but inter-observer variations pose a number of problems. A recent study has shown only moderate correlation between US and liver biopsy findings [11]. Moreover, many serum biomarkers and panels of combined markers have been studied worldwide, but most of them were established and used in chronic viral hepatitis [12–14] or alcoholic and non-alcoholic fatty liver disease [15,16]. Only one recent study has shown APRI, hyaluronic acid (HA) and tissue inhibitors of matrix metalloproteinases (TIMP)-1 were reliable and sensitive markers for differentiating significant liver fibrosis (F2-F4) in patients with advanced schistosomiasis japonica [17].

Thus, more efforts should be dedicated to search for noninvasive tools of liver fibrosis. In this study, we evaluated these routine laboratory tests for diagnosis of significant liver fibrosis, and constructed a new simple index to rapidly and effectively identify significant liver fibrosis in advanced schistosomiasis japonica patients.

2. Materials and methods

2.1. Patients

We studied advanced schistosomiasis japonica patients from the Nanhu and Xiuzhou region, Jiaxing City, Zhejiang Province, China. This region is endemic for *S. japonicum*. Fifty-two patients were selected from a total of 105 consecutive advanced schistosomiasis japonica patients who underwent a percutaneous liver biopsy in Jiaxing First Hospital, Zhejiang province, China from January 2011 to June 2012. Medical history and additional information on past water exposure to schistosomal infection were recorded for each individual. Laboratory examinations carried out for each patient included routine urine, stool and blood tests, liver and renal function tests, serology for schistosomal infection and for viral infections including hepatitis A, B, C and HIV. Exclusion criteria were as follows: (1) co-infection with hepatitis B virus, hepatitis C virus or human immunodeficiency virus and co-existent with non-alcoholic fatty liver disease; (2) alcohol consumption in excess of 20 g per day in men and excess of 10 g per day in women; (3) patients presenting with conditions relating to other vital organs. The study protocol was approved by Ethics Committee of Jiaxing First Hospital before study started. Patients were subsequently enrolled to the study after providing written informed consent.

2.2. Liver histology and quantification of fibrosis

Liver tissue was obtained by ultrasonography-guided percutaneous biopsy (Doctor Japan Co.Ltd) and stained with hematoylin–eosin–safran and Masson's trichrome. Fixed one blinded pathologist made diagnosis of fibrosis staging (F) according to the METAVIR system [18]. As the American Association for the Study of Liver Disease practice guidelines recommended, we defined significant liver fibrosis as METAVIR fibrosis score ≥ 2 (F2–F4) [19].

2.3. Blood and serum bio-markers

Blood analysis was performed using standard methodologies. Following parameters, including red blood cell (RBC) counts, white blood cell (WBC) counts, hemoglobin (HB), platelet count (PLT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin (TB), albumin, blood urea nitrogen (BUN), serum creatinine (Scr), prothrombin time (PT) and international normalized ratio (INR) were assayed. AST, ALT, ALP, GGT, TB, albumin, BUN and Scr were tested with Hitachi 7600, Japan. PT and INR were tested with STA-Revolution, France. RBC, WBC, HB and PLT were tested with Abbott CELL-DYN 3700, USA. The reference value was 0–60 IU/L for ALT, 0–50 IU/L for AST, and 11 ~ 14.5 seconds for PT. HA, laminin (LN), IV collagen (IV-C) and III procollagen (PCIII) (Shanghai High Medical Biotech, Shanghai, China) concentrations were measured by enzyme linked immunosorbent assay. Markers of hepatitis virus included HBsAg, HBsAb, HBeAg, HBeAb, HBcAb (Abbott Co., Shanghai, China), HBV-DNA (Shenyou Bio Tech Co., Ltd., Shanghai, China; sensitivity, 10^3copies/ml), anti-HCV, HCV RNA (Sino-American Bio Tech Co., Shanghai, China).

2.4. Ultrasonographic examinations

Ultrasound (US) apparatus used in this study was ALOKA ProSound SSD-3500 made in Japan. The pathological alteration of hepatic parenchyma was tested for all patients. US diagnosis of liver fibrosis in patients with advanced schistosomiasis japonica was classified to five types according to Chinese schistosomiasis control manual [20]. Grade 0, almost normal findings; Grade 1, some echogenic spots, bands, and/or nodules; Grade 2, fish-scale or network pattern with normal vessel; Grade 3, network pattern with wall thickness of portal vessel and thinning of intrahepatic vascular; Grade 4, changes of surface, nodules, liver atrophy.

2.5. Data management and statistical analysis

Results were expressed as mean values ± SD or median (interquartile range). One-way ANOVA tests or independent-sample *t*-tests were used for comparing the markers among groups. Significant variables from the univariate analysis ($P \leq 0.05$) were then subjected to multivariate analysis by forward logistic regression to identify independent factors associated with either end point. Significant fibrosis was considered as positive result and absence of significant fibrosis as a negative result. Variables with more than two classes were tested as binary variables in the regression models. A predictive index was constructed by modeling the values of the independent variables. The diagnostic values of parameters were assessed by calculating the area under receiver operating characteristic curves (AUROC). Optimal cutoff points were selected according to the best Youden index. The diagnostic accuracy was calculated using sensitivity, specificity, positive and negative predictive values (NPV and PPV), considering significant fibrosis as the disease. All data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, USA).

3. Results

3.1. Patient characteristics

The mean age of the 52 patients (23 males, 29 females) was 66.4 ± 9.1 years (range 44 to 88). The mean disease duration was 47.0 ± 6.9 years. No current infection of *S. japonicum* was found in stool examinations. And all of the 52 patients have taken praziquantel treatments when they were diagnosed of *S. japonicum* infections during 1960s to 1970s. Mean length of liver biopsies was 17.0 ± 2.4 mm, and all liver specimen length was longer than 15 mm. Significant liver fibrosis was found in 40 patients (76.9%) and early cirrhosis in 6 patients (11.5%), respectively. The US fibrosis score spectrum was as follows: 1 patient with Grade 0, 5 patients with Grade 1, 16 patients with Grade 2, 26 patients with Grade 3, and 4 patients with Grade 4. Main features of the patients are summarized in Table 1.

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